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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,724	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,80-82,85,91-104,107,110,111,115 and 121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,80-82,85,91-104,107,110,111,115 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed May 8, 2006 in response to the Office Action of February 8, 2006 is acknowledged and has been entered. Previously pending claims 71, 76-79, 84, 105, 106, 108, and 109 have been cancelled and claims 31,85,92-95, 102-104, 110, and 121 have been amended. Claims 31, 80-82, 85, 91-104,107, 110,111, 115, and 121 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC ' 112

4. Claims 31, 80-82, 85, 91-104,107, 110, 111, 115, and 121 remain rejected under 35 USC 112 1st for lacking enablement for a method for inhibiting an immune response for all recited products except an antibody specific for the alpha 2 macroglobulin receptor for the reasons previously set forth in the Office Action of February 8, 2006.

Applicant argues in the Amendment of May 8, 2006, as drawn to an α2M receptor fragment, that the specification provides a specific example of an α2M receptor fragment, the p80 fragment, which binds to heat shock proteins. Applicant argues that the specification at page 71-72 describes cross-linking and affinity purification experiments showing that gp96 binds to the p80 fragment of the α2M receptor (see also the specification at 73, lines 13- 19, identifying the p80 fragment as an amino terminal fragment of the α2M receptor). Applicant argues that the specification also demonstrates that the p80 fragment is involved in the interaction between heat

shock proteins and the α2M receptor which results in representation of heat shock protein-chaperoned antigenic peptide and applicant points to the example at pages 72-73 of the specification showing that antibodies raised against the p80 fragment of the α2M receptor inhibited representation of gp96-chaperoned antigenic peptides. Thus, applicant argues, that the p80 fragment both binds to heat shock protein and is involved in the a2M receptor immune activity. Applicant argues that exemplary α2M receptor fragments are disclosed in the specification and points to SEQ NOs: 20-22, 54-57, and the p80 α2M receptor fragment on p.10 of the Amendment of June 9, 2005 and that it was within the routine skill in the art to identify additional fragments of the α2M receptor that interfere with the interaction between heat shock proteins and the α2M receptor.

The arguments have been considered, but have not been found persuasive because the exemplified binding experiments are not commensurate in scope with the claimed invention because none of the claims are drawn to a method of inhibiting an immune response in a human comprising administering to a human a polypeptide consisting of the p80 fragment of the α2M receptor.

Further, although applicant suggests that it was within the skill of the art and routine to screen for the fragments that function as claimed, the screening assays taught and exemplified in the specification do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention since they are merely a wish or plan for obtaining the claimed chemical invention. Applicant is reminded that 35 USC 112 first paragraph does not require that the

specification teach how to "screen" for the claimed invention, rather 35 USC 112 first paragraph requires that requires that the specification teach how to **make** the claimed invention. It is clear from applicant's suggestion that the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the α2M receptor from those that will not. Since the making of the broadly claimed invention is not enabled, one would not know how to use the broadly claimed invention.

Applicant argues that the ability of a compound to inhibit a CTL response in an *in vitro* representation assay was accepted in the art at the time of filing as reasonably predictive of the ability to inhibit an *in vivo* immune response and points to the submitted Binder and Srivastava references which are drawn to in vivo assays with antibody against α2M receptor. The argument has been considered, but has not been found persuasive because the ability of α2M receptor fragments to inhibit CTL response has not been shown. Further, the references are not drawn to receptor fragments, but rather to a single antibody antagonist, anti-CD91 antibody. Further, it is clear that the art did not accept that the ability of any compound to inhibit a CTL response in an *in vitro* representation assay because the invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001) and the art clearly required objective evidence to demonstrate that the anti-CD91 antibody would function as suggested *in vivo*, that is to inhibit CD91 presentation of antigen that had not been previously presented.

Applicant argues in the Amendment of May 8, 2006, as drawn to an α2M fragment, that the example at page 73, lines 20-28 of the specification demonstrates that α2M, known in the art to be a ligand for the α2M receptor, was able to inhibit representation of a gp96-chaperoned antigenic peptide. Applicant argues that it follows that a fragment of α2M, which inhibits the interaction of a heat shock protein with the α2M receptor, would also inhibit representation of a heat shock protein-chaperoned antigenic peptide.

Applicant argues that exemplary α2M fragments, SEQ ID NO: 8-19, are taught in the specification and that the α2M receptor binding domain amino acids 1314-1451 is provided as described on p. 9 of the Amendment of June 9, 2005. Applicant argues that it was within the routine skill in the art to identify fragments of α2M that interfere with the interaction between heat shock proteins and the α2M receptor using the guidance provided in the specification and in view of the exemplary α2M fragments.

The arguments have been considered but have not been found persuasive because the exemplified experiments are not commensurate in scope with the claimed invention and although applicant opines that "it follows that a fragment of α2M which inhibits the interaction of a heat shock protein with the α2M receptor would also inhibit representation of a heat shock protein-chaperoned antigenic peptide, given the unpredictability of the art, in the absence of objective evidence no one of skill would believe it more likely than not that the invention would function as claimed.

Further, although applicant suggests that it was within the skill of the art and routine to screen for the fragments that function as claimed, the screening assays taught and

exemplified in the specification do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention since they are merely a wish or plan for obtaining the claimed chemical invention. Applicant is reminded that 35 USC 112 first paragraph does not require that the specification teach how to "screen" for the claimed invention, rather 35 USC112 first paragraph requires that requires that the specification teach how to **make** the claimed invention. It is clear from applicant's suggestion that the specification does **not** provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the α2M receptor from those that will not. Since the making of the broadly claimed invention is not enabled, one would not know how to use the broadly claimed invention.

Applicants argue in their Amendment mailed November 8,2004, that they presented post-filing evidence to support their position that the ability of a compound to inhibit a CTL response in an *in vitro* representation assay such as those described by the specific examples in the specification was reasonably predictive of the ability of the compound to inhibit an immune response in *vivo* (see Binder and Srivastava, 2004 IDS). Applicants argue that in their Amendment mailed June 9, 2005, they presented evidence that the state of the art in 1995 demonstrated a correlation between the ability of heat shock protein-peptide complexes to stimulate cytotoxic T-lymphocytes ("CTL") in an *in vitro* representation assay and the ability to elicit a CTL response *in vivo* (see Suto and Srivastava, 1995, and Binder *et al.*, 2002, IDS). Applicants argue that the ability of a compound to modulate a CTL response in an *in vitro*

representation assay was accepted in the art at the time of filing as reasonably predictive of the ability to modulate similarly an *in vivo* immune response.

The arguments have been considered, but has not been found persuasive because Binder et al. (2002, 2004, IDS) teach one example where administration of anti-CD91 antibody inhibited an immune response in a mouse model, but did not exemplify inhibition of immune response with any α2M fragments or α2M receptor fragments, see Binder 2002, Fig 3 and Binder 2004 Fig. 5. However, Binder et al. (2004, IDS) consider their results as "suggestive of a role of HSP-CD91 interaction in the human immune system and require further interrogation with more precise experimental strategies" (page 6133, right column, last sentence). The post-filing evidence does not teach which, if any, fragments of α2M or the α2M receptor can interfere with a heat shock protein interaction with the α2M receptor in vitro or in vivo. Thus the post-filing evidence is not commensurate in scope with the claims. Furthermore, Bellone et al. (1999, Immunology Today 20:457, cited in Office Action of 2/8/2006) summarize the current state of the art of peptide immunotherapy as ".,.a poor correlation between induction of specific T-cells and the clinical responses". Thus it would require undue experimentation for one of ordinary skill in the art to make and use a fragment of α2M or the α2M receptor for a method for inhibiting an immune response in a human by interfering with the interaction of a heat shock protein with the α2M receptor.

Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

5. All other objections and rejections set forth in the previous office action are hereby withdrawn.

6. Claims 31, 80-82, 85, 91-104,107, 110, 111, 115, and 121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified compound selected from the group consisting of an alpha (2) macroglobulin fragment, and an alpha (2) macroglobulin receptor fragment, and an antibody specific for the alpha (2) macroglobulin receptor, which compound interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor, and is in an amount effective to inhibit the immune response of said human.

This means that an alpha (2) macroglobulin fragment, an alpha (2) macroglobulin receptor fragment any alpha (2) macroglobulin fragment, and an antibody specific for the alpha (2) macroglobulin receptor can interfere with the interaction of heat shock protein with the alpha (2) macroglobulin receptor and inhibit an immune response in a human in need thereof.

The specification teaches that the invention provides a method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a purified compound that interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor. The specification teaches that in one embodiment of this method the compound in an antagonist that interferes with the interaction between the heat shock protein and the α2M receptor, p. 9, lines 30-35.

This means that although the claims are drawn to inhibiting an immune response in a human comprising administering the inhibiting agent in an amount effective to inhibit the immune response, that the claims read on a method of treating a disorder/immune disorder by administering an effective amount of the inhibiting agent.

One cannot extrapolate the teachings of the specification to the enablement of the claims because neither the specification nor the art of record has established a nexus between administering any of the claimed molecules to inhibiting an immune response in an autoimmune disorder given that it is well known in the art that in autoimmune disorders the immune system is already activated and that novel treatments are unpredictable of novel treatments in *in vivo* systems.

In particular, Janeway et al (Immunbiology, Ch. 13 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookH

L&term=autoimmune+AND+imm%5Bbook%5D+AND+125796%5Buid%5D&rid=imm.section.1906#1918) teach that in an autoimmune disease the individual's T cells are in an active state due to reactivity to self antigen, see 2nd paragraph.

Given that T cells are already in an active state in patients with an autoimmune disease one of skill in the art would not predict that interference with the interaction of heat shock proteins with the α2M receptor would predictably have any therapeutic affect on the autoimmune disorder or that it could inhibit an immune response in an autoimmune patient who already has activated T-cells. The effects of inhibiting CD91 interaction with HSPs cannot be predicted because it appears from Binder et al, 2004 that this inhibitory step must take place prior to active representation of the peptides on antigen presenting cells (see Binder, 2004, figure 5)

Thus, in the absence of objective evidence that the claimed invention will function in the *in vivo* environment in a human to in fact effectively treat an autoimmune disease, one could not predict that the method as claimed would function as claimed in a human, given the known activation of immune system in autoimmune diseases and the unpredictability of the art in that the invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001). Thus, it would require undue experimentation to make and use the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24

(CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature or the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as claimed will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. If applicant were able to overcome the rejections set forth above, claims 31, 80-82, 85, 91-104,107, 110, 111, 115, and 121 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting an immune response comprising administering to a human in need thereof **polyclonal anti-CD91 antibody specific for the alpha (2) macroglobulin receptor,** which compound interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor, and is in an amount effective to inhibit the immune response of said human, does not reasonably provide enablement for a method for inhibiting an immune response comprising administering to a human in need thereof **any** purified antibody specific for the alpha (2) macroglobulin receptor, which interferes with the

interaction of a heat shock protein with the alpha (2) macroglobulin receptor, and is in an amount effective to inhibit the immune response of said human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified antibody specific for the alpha (2) macroglobulin receptor, which compound interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor, and is in an amount effective to inhibit the immune response of said human.

This means that although the claims are drawn to inhibiting an immune response in a human comprising administering the inhibiting agent in an amount effective to inhibit the immune response, that the claims read on a method of treating a disorder/immune disorder by administering an effective amount of the inhibiting agent.

Further this means that **any** antibody, including monoclonal antibodies specific for the alpha (2) macroglobulin receptor can interfere with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor and inhibit immune response.

The specification teaches that antiserum against the 80 kDa protein fragment of the α2M receptor inhibits re-presentation of a gp96-chaperoned antigenic peptide by RAW264.7 cells pulsed with gp96-chaperoned antigenic peptide as measured by the release of interferon gamma, para bridging p. 72-73 and Fig 2B. Additionally, the specification teaches that the α2M protein inhibits re-presentation of a gp96-chaperoned antigenic peptide by RAW264.7 pulsed with gp96-chaperoned antigenic peptide, see p. 73, lines 20-28.

The specification teaches that described herein are methods for the production of antibodies capable of specifically recognizing α2M receptor epitopes, HSP-α2M receptor complex epitopes or epitopes of conserved variants or peptide fragments of the receptor or receptor complexes. The specification teaches that such antibodies are useful for therapeutic and diagnostic methods of the invention, , p. 23, lines 6-13.

The specification teaches that such antibodies may include, but are not limited to, polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(abl), fragments, fragments produced by a Fab expression library, antiidiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above, see p. 23, lines 10-13.

The specification teaches that anti-α2M receptor complex antibodies may be used as a method for the inhibition of abnormal receptor product activity. Thus, such antibodies may, be utilized as .part of treatment methods for HSP-α2M receptor related disorders, *e.g.*, autoimmune disorders, p. 23, lines 19-22.

One cannot extrapolate the teachings of the specification to the scope of the claims because one cannot predict that **any** antibody, including monoclonal antibodies, specific for the α2M receptor can interfere with the interaction of a heat shock protein with α2M receptor in amount effective to inhibit an immune response in a human because of the unpredictability of a given antibody to function in a manner similarly to another given antibody although the antibodies are directed to the same target.

Even if an antibody is specific for the α2M receptor, it does not mean that the antibody will interfere with the interaction of a heat shock protein with the α2M receptor because it is well

known in the art that even antibodies that are specific to a given target may function differently. In particular, Harlow and Lane (Antibodies, A Laboratory Manual, 1988, Ch. 6, p.139-243) teach that, although in theory monoclonal antibodies can be used for all of the tasks for which polyclonal antibodies are used, in practice one cannot predict how a monoclonal antibody will function, see p. 142, first para., and Table 6.1. Further, Harlow and Lane teach that ". . . producing exactly the right set of monoclonal antibodies is often a difficult and laborious job,." (p. 142, first para). Furthermore, Varner (US 6,852,318 B1 May 7, 1999) teaches that two different monoclonal antibodies to the alpha 5 beta 1 integrin receptor function differently in inhibiting angiogenesis. One type of anti alpha 5 beta 1 monoclonal antibody can block angiogenesis while another cannot, see column 22. Thus, one of ordinary skill in the art would not predict with reasonable expectation of success that any antibody to the α2M receptor would interfere with the interaction of a heat shock protein with the α2M receptor and inhibit an immune response in a human. Neither the specification nor the art of record teach that a monoclonal antibody to the α2M receptor can be used in the claimed method to inhibit an immune response in a human by interfering with the interaction of a heat shock protein with the α2M receptor. Additionally, neither the specification nor the art of record teach what epitopes of the α2M receptor are to be targeted for interference by a monoclonal antibody, which are reagents with unique, chosen specificity, see Harlow and Lane p. 141, 4th para. Given the above, undue experimentation would be required to identify the domain of the α2M receptor to be targeted by the monoclonal antibody and then to isolate a monoclonal antibody that inteferes with the interaction of a heat shock protein with the α2M receptor to practice the method as broadly claimed.

The specification provides neither information nor guidance on how to use the broadly claimed antibodies. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 31, 80-82, 85, 91-93, 102, 107, 110, and 121 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 31, 80-82, 85, 91-93, 102, 107, 110, and 121 are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified antibody specific for the α2M receptor that interferes with the interaction of a heat shock protein with the α2M receptor. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by

disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, per Lilly by structurally describing a representative number of α2M receptor antibodies that interfere with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human required to practice the method of claim 1 in a manner that satisfies

either the Lilly or Enzo standards. The specification does not provide the complete structure of any an α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor does the specification provide any partial structure of such an α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor any physical or chemical characteristics of the α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses that the polyclonal rabbit serum to α2M receptor inhibits representation of a gp96 chaperoned peptide *in vitro*, see para. bridging p. 72 and 73 and Figure 2, this does not provide a description of α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that would satisfy the standard set out in Enzo.

The specification also fails to describe the α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human by the test set out in Lilly. The specification describes only the polyclonal rabbit serum to the α2M receptor. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that is required to practice the claimed invention. Since the specification fails to adequately describe the α2M receptor antibody that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, it also fails to adequately describe the method for inhibiting an immune response by interfering with the interaction of a heat shock protein with the α2M receptor.

9. Upon review and reconsideration the following rejections are being reimposed.

10. Claims 31, 80-82, 85, 91, 94, 95, 103, 107, 110, and 111 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 31, 80-82, 85, 91, 94, 95, 103, 107, 110, and 111 are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed

subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc.,

296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, per Lilly by structurally describing a representative number of α2M fragments that interfere with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human required to practice the method of claim 1 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor does the specification provide any partial structure of such an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor any physical or chemical characteristics of the α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses that the α2M protein interferes with the interaction of a heat shock protein with the α2M receptor, see p. 73 lines 20-28 and Fig. 4, this does not provide a description of α2M fragments that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that would satisfy the standard set out in Enzo.

The specification also fails to describe the α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human by the test set out in Lilly. The specification describes only the α2M protein. Therefore, it necessarily fails to describe a "representative number" of such species. In addition,

the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that is required to practice the claimed invention. Since the specification fails to adequately describe the α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, it also fails to adequately describe the method for inhibiting an immune response by interfering with the interaction of a heat shock protein with the α2M receptor.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. This case is analogous to Example 13 of the written description guidelines. Specifically, the examples indicates that when a genus is represented by a single species, the specification and the claims must provide distinguishing attributes that are shared by the members of the genus. In the instant case, the structure of α2M is well established in the art, however, neither the specification or the claims provide sufficient description of which portions of α2M are encompassed as fragments. Again, no structure function relationship has been made in the specification or the claims. No structural detail other than the minimum number of amino acids (i.e. for α2M) in the fragment is disclosed in the specification, no partial structure or core motifs are provided in the specification, and no functional activity that correlates structure and function are provided in the specification or in the

claims. Applicant's reliance on general structure (i.e. α2M receptor binding domain) is inadequate because specific not general disclosure is required, so that one of skill in the art can distinguish the product used from others in the same class and also to show in such full, clear, concise, and exact terms that the skilled artisan would recognize that the applicant was in possession of the genus claimed.

Therefore, the USC 112 1st paragraph written description rejection is reimposed.

11. Claims 31, 80-82, 85, 91, 96-99, 104, 107, 110, and 115 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 31, 80-82, 85, 91, 96-99, 104, 107, 110, and 115 are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by

disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the an α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, per Lilly by structurally describing a representative number of α2M receptor fragments that interfere with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human required to practice the method of claim 1 in a manner that satisfies

either the Lilly or Enzo standards. The specification does not provide the complete structure of any an α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor does the specification provide any partial structure of such an α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, nor any physical or chemical characteristics of the α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses that the 80kDa α2M receptor interacts with the gp96 heat shock protein, see p. 73 lines 13-19, this does not provide a description of α2M receptor fragments that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that would satisfy the standard set out in Enzo.

The specification also fails to describe the α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human by the test set out in Lilly. The specification describes only the 80-kDa α2M receptor fragment. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M

receptor and inhibits an immune response in vivo in a human that is required to practice the claimed invention. Since the specification fails to adequately describe the α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human, it also fails to adequately describe the method for inhibiting an immune response by interfering with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. This case is analogous to Example 13 of the written description guidelines. Specifically, the examples indicates that when a genus is represented by a single species, the specification and the claims must provide distinguishing attributes that are shared by the members of the genus. In regard to α2M receptor, the disclosure of a single species does not adequately represent the full breadth of α2M receptor fragments encompassed. Again, no structure function relationship has been made in the specification or the claims. No structural detail other than the minimum number of amino acids (i.e. for α2M) in the fragment is disclosed in the specification, no partial structure or core motifs are provided in the specification, and no functional activity that correlates structure and function are provided in the specification or in the claims. Applicant's reliance on general structure function (i.e, ability to bind α2M receptor) is inadequate because specific not general disclosure is required, so that one of skill in the art can distinguish the product used from others in the same class and also to show in such full, clear, concise, and exact terms that the skilled artisan would recognize that the applicant was in possession of the genus claimed.

Therefore, the USC 112 1st paragraph written description rejection is reimposed.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR